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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/051,412	01/17/2002	Uwe Joerg Ries	5/1313	9079
28505	7590	05/13/2004	EXAMINER	
BOEHRINGER INGELHEIM CORPORATION 900 RIDGEURY ROAD P. O. BOX 368 RIDGEFIELD, CT 06877			ANDERSON, REBECCA L	
		ART UNIT	PAPER NUMBER	
		1626		

DATE MAILED: 05/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)
	10/051,412	RIES ET AL.
	Examiner	Art Unit
	Rebecca L Anderson	1626

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 25 February 2004.
- 2a) This action is FINAL.                                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1-8 is/are pending in the application.
  - 4a) Of the above claim(s) 4 and 8 is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 1-3 and 5-7 is/are rejected.
- 7) Claim(s) 1-3 and 5-7 is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.
 

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  - a) All    b) Some \* c) None of:
    1. Certified copies of the priority documents have been received.
    2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
    3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: \_\_\_\_\_

## DETAILED ACTION

Claims 1-8 are currently pending in the instant application. Claims 1-3 and 5-7 are rejected, claims 1-3 and 5-7 are objected and claims 4 and 8 are withdrawn from further consideration as being drawn to non-elected inventions.

### *Election/Restrictions*

Applicant's election with traverse of Group I, claims 1-7 and the species of compound 4, 2-(3-carbamimidoyl-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-isobutyramide in the paper mailed 02 July 2003 is acknowledged. The traversal, in the paper filed 25 February 2004, is on the ground(s) that the generic concept should be broadened to the concept in the amended claims since groups such as thienyl, thiazolyl, pyrimidyl, etc. are all monocyclic heteroaromatic groups and thus are clearly homologous with regard to search of prior art, since the functional groups of A exhibit similar IC50 values and since the values of R2 have similar IC50 values. This is not found persuasive because the withdrawn compounds which are withdrawn from consideration as being for non elected subject matter differ materially in structure and composition from the compounds of the elected invention. The withdrawn compounds differ from those of the elected invention such as by thienyl, thiazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, etc. which are chemically recognized to differ in structure and function. This recognized chemical diversity of the functional groups can be seen by the various classification of these functional groups in the U.S. classification system, i.e. class 549 subclass 29(+) (thienyl), class 548 subclass 146(+) (thiazolyl), class 544 subclass 242(+) (pyrimidinyl), class 544 subclass 336(+) (pyrazinyl), class 544 subclass

(224(+)) (pyridazinyl), etc. Therefore, again, the compounds which are withdrawn from consideration as being for non elected subject matter differ materially in structure and composition and have been restricted properly as a reference which anticipated but the elected subject matter would not even render obvious the non-elected subject matter.

These withdrawn compounds are independent and distinct from the elected invention and do not have unity with the species elected and are therefore withdrawn by means of a restriction requirement within the claims. Applicants' claims involve more than one independent or distinct invention. Under 35 U.S.C. 121, the claims may be restricted and the examination limited to a restricted invention. The withdrawn subject matter of claims 1-8 is properly restricted as it differs materially in structure and element from the elected subject matter identified *supra* so as to be patentably distinct there from. A reference, which anticipated but the elected subject matter would not even render obvious the non-elected subject matter. Accordingly, restriction, as has been required is proper.

Therefore, as stated in the previous action, the election of compound 4, 2-(3-carbamimidoyl-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-isobutyramide has resulted in the following generic concept: The product of the formula (I) wherein:

R1 denotes pyrrolidinocarbonyl

R2 denotes a hydrogen atom or an (unsubstituted) C1-3 alkyl group,

R3 denotes a hydrogen atom or a C1-3-alkyl group,

R4 denotes a hydrogen atom or an (unsubstituted) C1-3-alkyl group,

Ar denotes a phenyl group substituted by the groups R5, R6 and R7,

R5 denotes an (unsubstituted) amidino group,

R6 denotes a hydrogen atom or a C1-3-alkyl group,

R7 denotes a hydrogen atom or a C1-3-alkyl group,

R8 denotes a hydrogen atom or an (unsubstituted) C1-3-alkyl group and

R9 denotes a hydrogen atom or an (unsubstituted) C1-3-alkyl group.

The remaining subject matter of claims 1-3 and 5-7 that is not drawn to the elected invention identified *supra* and claims 4 and 8 stand withdrawn from consideration as being drawn to a non-elected invention, 37 CFR 1.142 (b).

The requirement is still deemed proper and is therefore made FINAL.

***Response to arguments and amendments***

Applicant's amendment to the claims filed 25 February 2004 has not deleted all of the non-elected subject matter from the claims and therefore has not overcome the objection to the claims as containing non-elected subject matter.

Applicant's amendment to the claims has deleted the specific compounds listed in claims 1-3 and has therefore overcome the 35 USC 112 2<sup>nd</sup> paragraph indefinite rejection of the claims.

Applicant's arguments filed 25 February 2004 have been fully considered but they are not persuasive. Applicant argues that the subject matter of the present invention is in no way obvious in view of example 24 of WO 00/71512, neither alone nor in combination with other embodiments disclosed in WO 00/71512. Applicant argues that example 24 of WO 00/71512 in no way teaches nor suggests the second substituent R2 at the phenylene group of the claimed compounds. This argument is not

found persuasive since the claims have been rejected over the entire reference as a whole. The prior art reference generically encompasses that which is instantly claimed and provides preferences towards the compounds as instantly claimed, specifically the prior art reference provides preferences for a substituted phenylene on page 24 wherein

### **Maintained Claim Objections**

Claims 1-3 and 5-7 are objected to as containing non-elected subject matter.

### **Maintained Claim Rejections - 35 USC § 103**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness. .

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1-3 and 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/71512.

Applicant's instant elected invention of claims 1-7 teach the compound of formula (I) wherein:

R1 denotes pyrrolidinocarbonyl,

R2 denotes a hydrogen atom or an (unsubstituted) C1-3 alkyl group,

R3 denotes a hydrogen atom or a C1-3-alkyl group,

R4 denotes a hydrogen atom or an (unsubstituted) C1-3-alkyl group,

Ar denotes a phenyl group substituted by the groups R5, R6 and R7,

R5 denotes an (unsubstituted) amidino group,

R6 denotes a hydrogen atom or a C1-3-alkyl group,

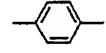
R7 denotes a hydrogen atom or a C1-3-alkyl group,

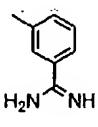
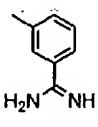
R8 denotes a hydrogen atom or an (unsubstituted) C1-3-alkyl group and

R9 denotes a hydrogen atom or an (unsubstituted) C1-3-alkyl group. (claim 1, 2) and wherein: R1 is in the 4 position of the phenyl group, R5 is in the 3 position if R6 denotes a hydrogen atom or position 5 if R6 is other than hydrogen (claim 3). Claim 5 teaches specific compounds such as 2-(3-carbamimidoyl-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-isobutyramide. Claim 6 teaches a physiologically acceptable salt of the compound of formula (I) and claim 7 teaches a pharmaceutical composition of the compound of formula (I).

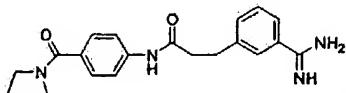
Determining the scope and contents of the prior art

The prior art WO 00/71512 discloses compounds of the formula A-Y-D-E-G-J-Z-L (pages 4) which are useful for the treatment of disease states (page 10) characterized by undesired thrombosis. Page 16 of the prior art discloses a preferred embodiment for the compound of formula A-Y-D-E-G-J-Z-L wherein G can be  $-CR_7R_8$ . A further preferred embodiment of the compound of formula A-Y-D-E-G-J-Z-L is found on page

31 wherein A can be  , Y can be  $-C(=O)-$ , D can be  or phenylene substituted with Cl, Br or methyl (page 24), E can be  $-N(H)-C(=O)-$ , J is a direct link

 (page 32), and Z-L can be  . Page 94 of the prior art reference discloses the compound of example 24:

Example 24. Preparation of N-[4-(1-pyrrolidinylcarbonyl)phenyl]-3-(3-amidinophenyl)-propionamide.



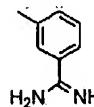
which has a value for A



corresponding to , a value for Y corresponding to  $-C(=O)-$ , a value for D



corresponding to , a value for E as  $-N(H)-C(=O)-$ , a value for J corresponding



to a direct link and a value for Z-L corresponding to . This species example disclose further preferences towards these specific values. Pages 14 and 15 of the prior art disclose pharmaceutically acceptable salts of the compounds of the formula A-Y-D-E-G-J-Z-L such as acid addition salts and base addition salts. Pages 53 and 54 disclose pharmaceutical compositions comprising the compound of the formula A-Y-D-E-G-J-Z-L and provides specific acceptable carriers, excipients and stabilizers and a preferred dosage.

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art and the instant elected invention is that the prior art does not disclose a specific species example which falls within applicants instant elected invention. The prior arts example 24 differs from the instantly elected invention in the value for G and D, but there are other preferred embodiments of the prior art invention which have the value for G as  $-CR_7R_8$  as discussed above.

Furthermore, the preferred embodiment of G as discussed above provides for only two possible substituents for the value of G, which provide motivation to prepare compounds with both of the possible substituents. The prior art also discloses preferred embodiments of the value of D wherein the phenylene is substituted with, for example, Cl, Br or methyl. Also, the prior art does generically disclose the compound of A-Y-D-E-G-J-Z-L which encompasses applicants instant invention and provides ample direction and guidance in the form of preferred embodiments as to the preferred substituents for A, Y, D, E, G, J, Z and L.

Resolving the level of ordinary skill in the pertinent art and considering objective evidence present in the application indicating obviousness or nonobviousness

Minus a showing of unobvious results, it would have been obvious to one of ordinary skill in the art at the time of the invention to create compounds which fall within applicants elected invention in order to prepare more compounds as found in the prior art of WO 00/71512 for antithrombotic treatment. The motivation is found in the prior art of WO 00/71512 which provides ample direction and guidance in the form of preferred embodiments and specific examples, and therefore, provides the motivation to prepare the compounds of applicants instant elected invention since these are the preferred compounds of WO 00/71512. The motivation is to prepare more compounds which are useful for antithrombotic treatment.

***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (571) 272-0696. Mrs. Anderson can normally be reached Monday through Friday 5:30AM to 2:00PM.

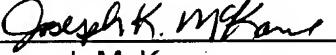
If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph McKane, can be reached at (571-272-0699).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone numbers are (703) 308-1235 and (703) 308-0196.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45AM to 4:45PM. The telecopier number for accessing the facsimile machine is (703) 872-9306

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

  
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